Complete Summary

GUIDELINE TITLE

Diseases characterized by genital ulcers. Sexually transmitted diseases treatment guidelines 2002.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Diseases characterized by genital ulcers. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2002 May 10;51(RR-6):11-25.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Sexually transmitted diseases characterized by genital ulcers, including chancroid, genital herpes simplex, granuloma inguinale (Donovanosis), lymphogranuloma venereum, and syphilis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases

Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To update the 1998 Guidelines for Treatment of Sexually Transmitted Diseases (MMWR 1998;47[No. RR-1])
- To assist physicians and other health-care providers in preventing and treating sexually transmitted diseases (STDs)
- To present updated recommendations for the diagnosis and management of sexually transmitted diseases characterized by genital ulcers

TARGET POPULATION

Patients with sexually transmitted diseases (STDs) characterized by genital ulcers, including pregnant women, infants and children exposed to infections during birth, individuals with co-existing human immunodeficiency virus (HIV) infection, and sex partners of infected individuals

INTERVENTIONS AND PRACTICES CONSIDERED

Note from the National Guideline Clearinghouse and the Centers for Disease Control and Prevention: These guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are important in sexually transmitted disease/human immunodeficiency virus (STD/HIV) prevention.

Diagnosis

1. Darkfield examination or direct immunofluorescence test for Treponema pallidum
2. Serologic tests for syphilis: nontreponemal (Venereal Disease Research Laboratory [VDRL]) and rapid plasma reagin [RPR]) and treponemal (fluorescent treponemal antibody absorbed [FTA-ABS]and T. pallidum particle agglutination)
3. Cerebrospinal fluid (CSF) cell count or protein (neurosyphilis)
4. Venereal Disease Research Laboratory-cerebrospinal fluid and cerebrospinal fluid fluorescent treponemal antibody absorbed (neurosyphilis)

5. Virologic (culture, polymerase chain reaction) and type-specific (immunoglobulin G-based) tests for herpes simplex virus
6. Culture for Haemophilus ducreyi
7. Visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy (diagnosis of Donovanosis)
8. Serological test for Chlamydia trachomatis
9. HIV testing
10. Skin testing for penicillin allergy

Drug treatment

Chancroid

1. Azithromycin
2. Ceftriaxone
3. Ciprofloxacin
4. Erythromycin base

Genital herpes simplex virus infection

1. Acyclovir
2. Famciclovir
3. Valacyclovir

Granuloma inguinale

1. Trimethoprim-sulfamethoxazole
2. Doxycycline
3. Ciprofloxacin
4. Erythromycin base
5. Azithromycin

Lymphogranuloma venereum

1. Doxycycline
2. Erythromycin base

Syphilis

1. Parenteral penicillin G preparations (benzathine, aqueous procaine, aqueous crystalline)

Other treatment/management considerations

1. Special considerations in pregnancy and in perinatal exposure to infections
2. Special consideration in HIV-infected persons
3. Special considerations in penicillin allergy, including alternative pharmaceutical agents and desensitization
4. Management of sex partners, including education, counseling, and treatment
5. Counseling of infected persons and their sex partners
6. Follow-up

7. Management of allergic and other adverse reactions

MAJOR OUTCOMES CONSIDERED

- Microbiologic cure
- Alleviation of signs and symptoms
- Prevention of sequelae
- Prevention of transmission

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Beginning in 2000, Centers for Disease Control and Prevention (CDC) personnel and professionals knowledgeable in the field of sexually transmitted diseases (STDs) systematically reviewed literature (i.e., published abstracts and peer-reviewed journal articles) concerning each of the major STDs, focusing on information that had become available since publication of the 1998 Guidelines for Treatment of Sexually Transmitted Diseases. Background papers were written and tables of evidence constructed summarizing the type of study (e.g., randomized controlled trial or case series), study population and setting, treatments or other interventions, outcome measures assessed, reported findings, and weaknesses and biases in study design and analysis. A draft document was developed on the basis of the reviews.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Centers for Disease Control and Prevention (CDC): When more than one therapeutic regimen is recommended, the sequence is alphabetized unless the choices for therapy are prioritized based on efficacy, convenience, or cost. For sexually transmitted diseases (STDs) with more than one recommended regimen, almost all regimens have similar efficacy and similar rates of intolerance or toxicity unless otherwise specified.

Management of Patients Who Have Genital Ulcers

In the United States, most young, sexually active patients who have genital ulcers have either genital herpes, syphilis, or chancroid. The relative frequency of each differs by geographic area and patient population; however, genital herpes is the most prevalent of these diseases. More than one of these diseases sometimes is present in a patient who has genital ulcers. Each disease has been associated with an increased risk for human immunodeficiency virus (HIV) infection. Not all genital ulcers are caused by sexually transmitted infections.

A diagnosis based only on the patient's medical history and physical examination often is inaccurate. Therefore, evaluation of all patients who have genital ulcers should include a serologic test for syphilis and a diagnostic evaluation for genital herpes; in settings where chancroid is prevalent, a test for Haemophilus ducreyi should also be performed. Specific tests for evaluation of genital ulcers include:

- serology, and either darkfield examination or direct immunofluorescence test for T. pallidum
- culture or antigen test for herpes simplex virus (HSV)
- culture for H. ducreyi

No Food and Drug Administration (FDA)-approved polymerase chain reaction (PCR) test for these organisms is available in the United States, but such testing can be performed by commercial laboratories that have developed their own polymerase chain reaction tests. Type-specific serology for HSV type 2 may be helpful in identifying persons with genital herpes (see section on "Genital Herpes" below). Biopsy of ulcers may be helpful in identifying the cause of unusual ulcers or ulcers that do not respond to initial therapy.

HIV testing should be performed in the management of patients who have genital ulcers caused by T. pallidum or H. ducreyi. Such testing should be considered for those who have ulcers caused by HSV (see section on "Syphilis", "Chancroid", and "Genital Herpes" below).

Health-care providers often must treat patients before test results are available because early treatment decreases the possibility of ongoing transmission and because successful treatment of genital herpes depends upon prompt initiation of therapy. In this circumstance, the clinician should treat for the diagnosis considered most likely on the basis of clinical presentation and epidemiologic circumstances. Sometimes treatment must be initiated for additional conditions because of diagnostic uncertainty. Even after complete diagnostic evaluation, at least 25% of patients who have genital ulcers have no laboratory-confirmed diagnosis.

Chancroid

In the United States, chancroid usually occurs in discrete outbreaks, although the disease is endemic in some areas. Chancroid is a cofactor for HIV transmission; high rates of HIV infection among patients who have chancroid occur in the United States and other countries. About 10% of persons who have chancroid acquired in the United States are coinfected with T. pallidum or HSV; this percentage is higher in persons acquiring chancroid outside the United States.

A definitive diagnosis of chancroid requires identification of H. ducreyi on special culture media that is not widely available from commercial sources; even using these media, sensitivity is $\leq$80%. No FDA-approved polymerase chain reaction test for H. ducreyi is available in the United States, but such testing can be performed by commercial laboratories that have developed their own polymerase chain reaction test. A probable diagnosis, for both clinical and surveillance purposes, can be made if all the following criteria are met: a) the patient has one or more painful genital ulcers; b) the patient has no evidence of T. pallidum infection by darkfield examination of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; c) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; and d) a test for HSV performed on the ulcer exudate is negative. The combination of a painful ulcer and tender inguinal adenopathy, symptoms occurring in one third of patients, suggests a

diagnosis of chancroid; when accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.

Treatment

Successful treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, scarring can result despite successful therapy.

Recommended Regimens

- Azithromycin 1 g orally in a single dose

  OR

- Ceftriaxone 250 mg intramuscularly (IM) in a single dose

  OR

- Ciprofloxacin 500 mg orally twice a day for 3 days

  OR

- Erythromycin base 500 mg orally three times a day for 7 days

Note: Ciprofloxacin is contraindicated for pregnant and lactating women.

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported.

Other Management Considerations

Patients who are uncircumcised and patients with HIV infection do not respond as well to treatment as those who are circumcised or HIV-negative. Patients should be tested for HIV infection at the time chancroid is diagnosed. Patients should be retested for syphilis and HIV 3 months after the diagnosis of chancroid if the initial test results were negative.

Follow-Up

Patients should be re-examined 3-7 days after initiation of therapy. If treatment is successful, ulcers usually improve symptomatically within 3 days and objectively within 7 days after therapy. If no clinical improvement is evident, the clinician must consider whether a) the diagnosis is correct, b) the patient is coinfected with another STD, c) the patient is infected with HIV, d) the treatment was not used as instructed, or e) the H. ducreyi strain causing the infection is resistant to the prescribed antimicrobial. The time required for complete healing depends on the size of the ulcer; large ulcers may require >2 weeks. In addition, healing is slower for some uncircumcised men who have ulcers under the foreskin. Clinical

resolution of fluctuant lymphadenopathy is slower than that of ulcers and may require needle aspiration or incision and drainage, despite otherwise successful therapy. Although needle aspiration of buboes is a simpler procedure, incision and drainage may be preferred because of reduced need for subsequent drainage procedures.

Management of Sex Partners

Sex partners of patients who have chancroid should be examined and treated, regardless of whether symptoms of the disease are present, if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

Special Considerations

Pregnancy

The safety and efficacy of azithromycin for pregnant and lactating women have not been established. Ciprofloxacin is contraindicated during pregnancy and lactation. No adverse effects of chancroid on pregnancy outcome have been reported.

HIV Infection

HIV-infected patients who have chancroid should be monitored closely because, as a group, these patients are more likely to experience treatment failure and to have ulcers that heal more slowly. HIV-infected patients may require longer courses of therapy than those recommended for HIV-negative patients, and treatment failures can occur with any regimen. Because data are limited concerning the therapeutic efficacy of the recommended ceftriaxone and azithromycin regimens in HIV-infected patients, these regimens should be used for such patients only if follow-up can be ensured. Some specialists suggest using the erythromycin 7-day regimen for treating HIV-infected persons.

Genital Herpes Simplex Virus Infections

Genital herpes is a recurrent, life-long viral infection. Two serotypes of HSV have been identified: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2. At least 50 million persons in the United States have genital HSV infection.

Most persons infected with HSV-2 have not been diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. Most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. Rarely, first-episode genital herpes is manifested by severe disease that may require hospitalization.

Diagnosis of HSV Infection

The clinical diagnosis of genital herpes is both insensitive and nonspecific. The typical painful multiple vesicular or ulcerative lesions are absent in many infected persons. Up to 30% of first-episode cases of genital herpes are caused by HSV-1, but recurrences are much less frequent for genital HSV-1 infection than genital HSV-2 infection. Therefore, the distinction between HSV serotypes influences prognosis and counseling. For these reasons, the clinical diagnosis of genital herpes should be confirmed by laboratory testing. Both virologic tests and type-specific serologic tests for HSV should be available in clinical settings that provide care for patients with sexually transmitted diseases or those at risk for sexually transmitted diseases.

Virologic Tests

Isolation of HSV in cell culture is the preferred virologic test in patients who present with genital ulcers or other mucocutaneous lesions. The sensitivity of culture declines rapidly as lesions begin to heal, usually within a few days of onset. Some HSV antigen detection tests, unlike culture and the direct fluorescent antibody test, do not distinguish HSV-1 from HSV-2. Polymerase chain reaction (PCR) assays for HSV deoxyribonucleic acid (DNA) are highly sensitive, but their role in the diagnosis of genital ulcer disease has not been well-defined. However, polymerase chain reaction is available in some laboratories and is the test of choice for detecting HSV in spinal fluid for diagnosis of HSV-infection of the central nervous system (CNS). Cytologic detection of cellular changes of herpes virus infection is insensitive and nonspecific, both in genital lesions (Tzanck preparation) and cervical Papanicolaou (Pap) smears, and should not be relied on for diagnosis of HSV infection.

Type-specific Serologic Tests

Both type-specific and nonspecific antibodies to HSV develop during the first several weeks following infection and persist indefinitely. Because almost all HSV-2 infections are sexually acquired, type-specific HSV-2 antibody indicates anogenital infection, but the presence of HSV-1 antibody does not distinguish anogenital from orolabial infection. Accurate type-specific assays for HSV antibodies must be based on the HSV-specific glycoprotein G2 for the diagnosis of infection with HSV-2 and glycoprotein G1 for diagnosis of infection with HSV-1. Such assays first became commercially available in 1999, but older assays that do not accurately distinguish HSV-1 from HSV-2 antibody, despite claims to the contrary, remain on the market. Therefore, the serologic type-specific gG-based assays should be specifically requested when serology is performed.

Currently, the FDA-approved, gG-based type-specific assays include POCkit™ HSV -2 (manufactured by Diagnology); HerpeSelect™ -1 enzyme-linked immunosorbent assay (ELISA) immunoglobulin G (IgG) or HerpeSelect™ -2 ELISA IgG (manufactured by Focus Technology, Inc.); and HerpeSelect™ 1 and 2 Immunoblot IgG (manufactured by Focus Technology, Inc.). The POCkit™ - HSV-2 assay is a point-of-care test that provides results for HSV-2 antibodies from capillary blood or serum during a clinic visit. The Focus Technology assays are laboratory-based. The sensitivities of these tests for detection of HSV-2 antibody vary from 80% to 98%, and false-negative results may occur, especially at early stages of infection. The specificities of these assays are $\geq$96%. False-positive results can occur, especially in patients with low likelihood of HSV infection.

Therefore, repeat testing or a confirmatory test (e.g., an immunoblot assay if the initial test was an enzyme-linked immunosorbent assay) may be indicated in some settings.

Because false-negative HSV cultures are common, especially in patients with recurrent infection or with healing lesions, type-specific serologic tests are useful in confirming a clinical diagnosis of genital herpes. Additionally, such tests can be used to diagnose persons with unrecognized infection and to manage sex partners of persons with genital herpes. Although serologic assays for HSV-2 should be available for persons who request them, screening for HSV-1 or HSV-2 infection in the general population is not indicated.

Principles of Management of Genital Herpes

Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. In addition, counseling regarding the natural history of genital herpes, sexual and perinatal transmission, and methods to reduce transmission is integral to clinical management.

Systemic antiviral drugs partially control the symptoms and signs of herpes episodes when used to treat first clinical episodes and recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. Randomized trials indicate that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir, a pro-drug of penciclovir, also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is not recommended.

First Clinical Episode of Genital Herpes

Many patients with first-episode herpes present with mild clinical manifestations but later develop severe or prolonged symptoms. Therefore, most patients with initial genital herpes should receive antiviral therapy.

Recommended Regimens

- Acyclovir 400 mg orally three times a day for 7-10 days

  OR

- Acyclovir 200 mg orally five times a day for 7-10 days

  OR

- Famciclovir 250 mg orally three times a day for 7-10 days

  OR

- Valacyclovir 1 g orally twice a day for 7-10 days

Note: Treatment may be extended if healing is incomplete after 10 days of therapy.

Higher dosages of acyclovir (i.e., 400 mg orally five times a day) were used in treatment studies of first-episode herpes proctitis and first-episode oral infection. However, no comparative studies have been conducted, and whether these forms of HSV infection require higher doses of antiviral drugs than used for genital herpes is unknown. Valacyclovir and famciclovir probably are also effective for acute HSV proctitis or oral infection, but clinical experience is lacking.

Recurrent Episodes of HSV Disease

Most patients with symptomatic, first-episode genital HSV-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are much less frequent following initial genital HSV-1 infection. Antiviral therapy for recurrent genital herpes can be administered either episodically, to ameliorate or shorten the duration of lesions, or continuously as suppressive therapy to reduce the frequency of recurrences. Many patients, including those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy; therefore, options for treatment should be discussed with all patients.

Episodic Therapy for Recurrent Genital Herpes

Effective episodic treatment of recurrent herpes requires initiation of therapy within 1 day of lesion onset, or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to self-initiate treatment immediately when symptoms begin.

Recommended Regimens

- Acyclovir 400 mg orally three times a day for 5 days

  OR

- Acyclovir 200 mg orally five times a day for 5 days

  OR

- Acyclovir 800 mg orally twice a day for 5 days

  OR

- Famciclovir 125 mg orally twice a day for 5 days

  OR

- Valacyclovir 500 mg orally twice a day for 3-5 days

  OR

- Valacyclovir 1.0 g orally once a day for 5 days.

For episodic therapy, a randomized controlled trial indicated that a 3-day course of valacyclovir 500 mg twice daily is as effective as a 5-day course. Similar studies have not been done with acyclovir and famciclovir.

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy reduces the frequency of genital herpes recurrences by 70%-80% among patients who have frequent recurrences (i.e., ≥6 recurrences per year), and many patients report no symptomatic outbreaks. Treatment probably is also effective in patients with less frequent recurrences, although definitive data are lacking. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years, and with valacyclovir or famciclovir for 1 year. Quality of life often is improved in patients with frequent recurrences who receive suppressive compared with episodic treatment.

The frequency of recurrent outbreaks diminishes over time in many patients, and the patient's psychological adjustment to the disease may change. Therefore, periodically during suppressive treatment (e.g., once a year), discontinuation of therapy should be discussed with the patient to reassess the need for continued therapy.

Suppressive antiviral therapy reduces but does not eliminate subclinical viral shedding. Therefore, the extent to which suppressive therapy prevents HSV transmission is unknown.

Recommended Regimens

- Acyclovir 400 mg orally twice a day

  OR

- Famciclovir 250 mg orally twice a day

  OR

- Valacyclovir 500 mg orally once a day

  OR

- Valacyclovir 1.0 gram orally once a day

Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year). Few comparative studies of valacyclovir or famciclovir with acyclovir have been conducted. The results of these studies suggest that valacyclovir and famciclovir are comparable to acyclovir in clinical outcome. Ease of administration and cost also are important considerations for prolonged treatment.

Severe Disease

Intravenous (IV) acyclovir therapy should be provided for patients who have severe disease or complications that necessitate hospitalization, such as disseminated infection, pneumonitis, hepatitis, or complications of the central nervous system (e.g., meningitis or encephalitis). The recommended regimen is acyclovir 5-10 mg/kg body weight intravenously every 8 hours for 2-7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days total therapy.

Counseling

Counseling of infected persons and their sex partners is critical to management of genital herpes. Counseling has two main goals: to help patients cope with the infection and to prevent sexual and perinatal transmission. Although initial counseling can be provided at the first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides. Numerous resources, including the CDC National STD/HIV Hotline (tel: 800-227-8922), Web site (www.ashastd.org), and printed materials are available to assist patients and clinicians in counseling.

HSV-infected persons may express anxiety about genital herpes that does not reflect the actual clinical severity of their disease; the psychological impact of infection often is substantial. Common concerns about genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children. The misconception that HSV causes cancer should be dispelled, because the role of HSV-2 in cervical cancer is at most that of a cofactor, not a primary etiologic agent.

Specific counseling messages should include the following information.

- Patients who have genital herpes should be educated about the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and attendant risks of sexual transmission.
- Patients experiencing a first episode of genital herpes should be advised that suppressive and episodic antiviral therapy is available and is effective in preventing or shortening the duration of recurrent episodes.
- All persons with genital HSV infection should be encouraged to inform their current sex partners that they have genital herpes and to inform future partners before initiating a sexual relationship.
- Persons with genital herpes should be informed that sexual transmission of HSV can occur during asymptomatic periods. Asymptomatic viral shedding is more frequent in genital HSV-2 infection than genital HSV-1 infection and is most frequent in the first 12 months of acquiring HSV-2.
- Patients should be advised to abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
- Latex condoms, when used consistently and correctly, can reduce the risk for genital herpes when the infected areas are covered or protected by the condom. A recent prospective study suggests that condoms have been effective in preventing transmission from men to women.

- Sex partners of infected persons should be advised that they might be infected even if they have no symptoms. Type-specific serologic testing of asymptomatic partners of persons with genital herpes can determine whether risk for HSV acquisition exists.
- The risk for neonatal HSV infection should be explained to all patients, including men. Pregnant women and women of childbearing age who have genital herpes should inform their providers who care for them during pregnancy as well as those who will care for their newborn infant. Pregnant women who are not infected with HSV-2 should be advised to avoid intercourse during the third trimester with men who have genital herpes. Similarly, pregnant women who are not infected with HSV-1 should be counseled to avoid genital exposure to HSV-1 during the third trimester (e.g., cunnilingus with a partner with oral herpes and vaginal intercourse with a partner with genital HSV-1 infection).
- Asymptomatic persons diagnosed with HSV-2 infection by type-specific serologic testing should receive the same counseling messages as persons with symptomatic infection. In addition, such persons should be taught about the common manifestations of genital herpes. Antiviral therapy is not recommended for persons who do not have clinical manifestations of infection.

Management of Sex Partners

The sex partners of patients who have genital herpes likely benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have genital lesions. Asymptomatic sex partners of patients who have genital herpes should be questioned concerning histories of genital lesions, educated to recognize symptoms of herpes, and offered type-specific serologic testing for HSV infection.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Allergic and other adverse reactions to acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described.

HIV Infection

Immunocompromised patients may have prolonged or severe episodes of genital, perianal, or oral herpes. Lesions caused by HSV are common among HIV-infected patients and may be severe, painful, and atypical. Episodic or suppressive therapy with oral antiviral agents is often beneficial.

Recommended Regimens for Episodic Infection in Persons Infected with HIV

- Acyclovir 400 mg orally three times a day for 5-10 days

  OR

- Acyclovir 200 mg five times a day for 5-10 days

  OR

- Famciclovir 500 mg orally twice a day for 5-10 days

  OR

- Valacyclovir 1.0 g orally twice a day for 5-10 days

Recommended Regimens for Daily Suppressive Therapy in Persons Infected with HIV

- Acyclovir 400-800 mg orally twice to three times a day

  OR

- Famciclovir 500 mg orally twice a day

  OR

- Valacyclovir 500 mg orally twice a day

In the doses recommended for treatment of genital herpes, acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients. For severe cases, initiating therapy with acyclovir 5-10 mg/kg body weight intravenously every 8 hours may be necessary.

If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate obtained for sensitivity testing. Such patients should be managed in consultation with a specialist, and alternate therapy should be administered. All acyclovir-resistant strains are resistant to valacyclovir and most are resistant to famciclovir. Foscarnet, 40 mg/kg body weight intravenously every 8 hours until clinical resolution is attained, is often effective for treatment of acyclovir-resistant genital herpes. Topical cidofovir gel 1% applied to the lesions once daily for 5 consecutive days also might be effective. This preparation is not commercially available and must be compounded at a pharmacy.

Genital Herpes in Pregnancy

Most mothers of infants who acquire neonatal herpes lack histories of clinically evident genital herpes. The risk for transmission to the neonate from an infected mother is high (30%-50%) among women who acquire genital herpes near the time of delivery and is low (<1%) among women with histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy. However, because recurrent genital herpes is much more common than initial HSV infection during pregnancy, the proportion of neonatal HSV infections acquired from mothers with recurrent herpes remains high. Prevention of neonatal herpes depends both on preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the infant to herpetic lesions during delivery.

Women without known genital herpes should be counseled to avoid intercourse during the third trimester with partners known or suspected of having genital herpes. In addition, pregnant women without known orolabial herpes should be advised to avoid cunnilingus during the third trimester with partners known or suspected to have orolabial herpes. Some specialists believe type-specific serologic tests are useful to identify pregnant women at risk for HSV infection and to guide counseling with regard to the risk of acquiring genital herpes during pregnancy. Such testing and counseling may be especially important when a woman's sex partner has HSV infection.

All pregnant women should be asked whether they have a history of genital herpes. At the onset of labor, all women should be questioned carefully about symptoms of genital herpes, including prodrome, and all women should be examined carefully for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Most specialists recommend that women with recurrent genital herpetic lesions at the onset of labor deliver by cesarean section to prevent neonatal herpes. However, abdominal delivery does not completely eliminate the risk for HSV transmission to the infant. The results of viral cultures during pregnancy in women with or without visible herpetic lesions do not predict viral shedding at the time of delivery, and therefore routine viral cultures of pregnant women with recurrent genital herpes are not recommended.

The safety of systemic acyclovir, valacyclovir, and famciclovir therapy in pregnant women has not been established. Available data do not indicate an increased risk for major birth defects compared with the general population in women treated with acyclovir during the first trimester. These findings provide some assurance to women who have had prenatal exposure to acyclovir. However, available data are insufficient to reach definitive conclusions regarding the risks to the newborn associated with acyclovir treatment during pregnancy. The experience with prenatal exposure to valacyclovir and famciclovir is too limited to provide useful information on pregnancy outcomes.

Acyclovir may be administered orally to pregnant women with first episode genital herpes or severe recurrent herpes and should be administered intravenously to pregnant women with severe HSV infection. Preliminary data suggest that acyclovir treatment late in pregnancy might reduce the frequency of cesarean sections among women who have recurrent genital herpes by diminishing the frequency of recurrences at term, and some specialists recommend such treatment. The risk for herpes is high in infants of women who acquire genital HSV in late pregnancy; such women should be managed in consultation with an HSV specialist. Some specialists recommend acyclovir therapy in this circumstance, some recommend routine cesarean section to reduce the risk for neonatal herpes, and others recommend both.

Neonatal Herpes

Infants exposed to HSV during birth, as documented by virologic testing or presumed by observation of lesions, should be followed carefully in consultation with a specialist. Some specialists recommend that such infants undergo surveillance cultures of mucosal surfaces to detect HSV infection before development of clinical signs of neonatal herpes. Some specialists recommend the

use of acyclovir for infants born to women who acquired HSV near term, because the risk for neonatal herpes is high for these infants.

All infants who have evidence of neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight intravenously every 8 hours for 21 days for disseminated and central nervous system disease, or 14 days for disease limited to the skin and mucous membranes.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale is a genital ulcerative disease caused by the intracellular Gram-negative bacterium Calymmatobacterium granulomatis. The disease occurs rarely in the United States, although it is endemic in certain tropical and developing areas, including India; Papua, New Guinea; central Australia; and southern Africa. Clinically, the disease commonly presents as painless, progressive ulcerative lesions without regional lymphadenopathy. The lesions are highly vascular ("beefy red appearance") and bleed easily on contact. However, the clinical presentation can also include hypertrophic, necrotic, or sclerotic variants. The causative organism is difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy. The lesions may develop secondary bacterial infection or may be coinfected with another sexually transmitted pathogen.

Treatment

Treatment halts progression of lesions, although prolonged therapy may be required to permit granulation and reepithelialization of the ulcers. Relapse can occur 6--18 months after apparently effective therapy. Several antimicrobial regimens have been effective, but few controlled trials have been published.

Recommended Regimens

- Doxycycline 100 mg orally twice a day for at least 3 weeks

  OR

- Trimethoprim-sulfamethoxazole one double-strength (800 mg /160 mg) tablet orally twice a day for at least 3 weeks

Alternative Regimens

- Ciprofloxacin 750 mg orally twice a day for at least 3 weeks

  OR

- Erythromycin base 500 mg orally four times a day for at least 3 weeks

  OR

- Azithromycin 1 g orally once per week for at least 3 weeks

Therapy should be continued at least 3 weeks or until all lesions have completely healed. Some specialists recommend addition of an aminoglycoside (e.g., gentamicin 1 mg/kg intravenously every 8 hours) to the above regimens if improvement is not evident within the first few days of therapy.

Follow-Up

Patients should be followed clinically until signs and symptoms have resolved.

Management of Sex Partners

Persons who have had sexual contact with a patient who has granuloma inguinale within the 60 days before onset of the patient's symptoms should be examined and offered therapy. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.

Special Considerations

Pregnancy

Pregnancy is a relative contraindication to the use of sulfonamides. Pregnant and lactating women should be treated with the erythromycin regimen, and consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin). Azithromycin may prove useful for treating granuloma inguinale in pregnancy, but published data are lacking. Doxycycline and ciprofloxacin are contraindicated in pregnant women.

HIV Infection

Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who are HIV negative. Consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin).

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by C. trachomatis serovars L1, L2, or L3. The disease occurs rarely in the United States. The most common clinical manifestation of lymphogranuloma venereum among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is most commonly unilateral. Women and homosexually active men may have proctocolitis or inflammatory involvement of perirectal or perianal lymphatic tissues resulting in fistulas and strictures. A self-limited genital ulcer sometimes occurs at the site of inoculation. However, by the time patients seek care, the ulcer usually has disappeared. The diagnosis of lymphogranuloma venereum is usually made serologically and by exclusion of other causes of inguinal lymphadenopathy or genital ulcers. Complement fixation titers $\geq$1:64 are consistent with the diagnosis of lymphogranuloma venereum. The diagnostic utility of serologic methods other than complement fixation is unknown.

Treatment

Treatment cures infection and prevents ongoing tissue damage, although tissue reaction can result in scarring. Buboes may require aspiration through intact skin or incision and drainage to prevent the formation of inguinal/femoral ulcerations. Doxycycline is the preferred treatment.

Recommended Regimen

- Doxycycline 100 mg orally twice a day for 21 days

Alternative Regimen

- Erythromycin base 500 mg orally four times a day for 21 days

Some STD specialists believe azithromycin 1.0 g orally once weekly for 3 weeks is likely effective, although clinical data are lacking.

Follow-Up

Patients should be followed clinically until signs and symptoms have resolved.

Management of Sex Partners

Persons who have had sexual contact with a patient who has lymphogranuloma venereum within the 30 days before onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated.

Special Considerations

Pregnancy

Pregnant and lactating women should be treated with erythromycin. Azithromycin may prove useful for treatment of lymphogranuloma venereum in pregnancy, but no published data are available regarding its safety and efficacy. Doxycycline is contraindicated in pregnant women.

HIV Infection

Persons with both lymphogranuloma venereum and HIV infection should receive the same regimens as those who are HIV-negative. Prolonged therapy may be required, and delay in resolution of symptoms may occur.

Syphilis

General Principles

Background

Syphilis is a systemic disease caused by T. pallidum. Patients who have syphilis may seek treatment for signs or symptoms of primary infection (i.e., ulcer or chancre at the infection site), secondary infection (i.e., manifestations that include but are not limited to skin rash, mucocutaneous lesions, and lymphadenopathy), or tertiary infection (e.g., cardiac, ophthalmic, auditory abnormalities, and gummatous lesions). Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration. Treatment for both late latent syphilis and tertiary syphilis theoretically may require a longer duration of therapy because organisms are dividing more slowly; however, the validity of this concept has not been assessed.

Diagnostic Considerations and Use of Serologic Tests

Darkfield examinations and direct fluorescent antibody tests of lesion exudate or tissue are the definitive methods for diagnosing early syphilis. A presumptive diagnosis is possible with the use of two types of serologic tests for syphilis: a) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and Rapid Plasma Reagin [RPR]) and b) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] and T. pallidum particle agglutination [TP-PA]). The use of only one type of serologic test is insufficient for diagnosis, because false-positive nontreponemal test results may occur secondary to various medical conditions.

Nontreponemal test antibody titers usually correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed by using the same testing method (e.g., VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers often are slightly higher than VDRL titers. Nontreponemal tests usually become nonreactive with time after treatment; however, in some patients, nontreponemal antibodies can persist at a low titer for a long period of time, sometimes for the life of the patient. This response is referred to as the "serofast reaction".

Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15%-25% of patients treated during the primary stage revert to being serologically nonreactive after 2-3 years. Treponemal test antibody titers correlate poorly with disease activity and should not be used to assess treatment response.

Some HIV-infected patients can have atypical serologic test results (i.e., unusually high, unusually low, or fluctuating titers). For such patients, when serologic tests and clinical syndromes suggestive of early syphilis do not correspond with one another, use of other tests (e.g., biopsy and direct microscopy) should be considered. However, for most HIV-infected patients, serologic tests are accurate and reliable for the diagnosis of syphilis and for following the response to treatment.

No test can be used alone to diagnose neurosyphilis. The VDRL–cerebrospinal fluid (CSF) is highly specific, but it is insensitive. Most other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, abnormalities of cerebrospinal fluid (CSF) cell count or protein, or a reactive VDRL-CSF with or without clinical manifestations. The CSF leukocyte count usually is elevated (>5 white blood cells/mm^3) in patients with neurosyphilis; this count also is a sensitive measure of the effectiveness of therapy. The VDRL-CSF is the standard serologic test for CSF, and when reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis. However, the VDRL-CSF may be nonreactive when neurosyphilis is present. Some specialists recommend performing an fluorescent treponemal antibody absorbed test on CSF. The CSF fluorescent treponemal antibody absorbed is less specific (i.e., yields more false-positive results) for neurosyphilis than the VDRL-CSF, but the test is highly sensitive. Therefore, some specialists believe that a negative CSF fluorescent treponemal antibody absorbed test excludes neurosyphilis.

Treatment

Penicillin G, administered parenterally, is the preferred drug for treatment of all stages of syphilis. The preparation(s) used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of disease. However, neither combinations of benzathine penicillin and procaine penicillin nor oral penicillin preparations are considered appropriate for the treatment of syphilis.

The efficacy of penicillin for the treatment of syphilis was well established through clinical experience before the value of randomized controlled clinical trials was recognized. Therefore, almost all the recommendations for the treatment of syphilis are based on the opinions of persons knowledgeable about STDs and are reinforced by case series, clinical trials, and 50 years of clinical experience.

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin. Skin testing for penicillin allergy may be useful in pregnant women; such testing also is useful in other patients.

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, and other symptoms that usually occurs within the first 24 hours after any therapy for syphilis. Patients should be informed about this possible adverse reaction. The Jarisch-Herxheimer reaction occurs most often among patients who have early syphilis. Antipyretics may be used, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress in pregnant women. This concern should not prevent or delay therapy (see Syphilis During Pregnancy).

Management of Sex Partners

Sexual transmission of T. pallidum occurs only when mucocutaneous syphilitic lesions are present; such manifestations are uncommon after the first year of infection. However, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically according to the following recommendations.

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., $\geq$1:32) can be assumed to have early syphilis. However, serologic titers should not be used to differentiate early from late latent syphilis for the purpose of determining treatment.
- Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.

For identification of at-risk partners, the time periods before treatment are a) 3 months plus duration of symptoms for primary syphilis, b) 6 months plus duration of symptoms for secondary syphilis, and c) 1 year for early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively for more than 50 years to achieve clinical resolution (i.e., healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no comparative trials have been adequately conducted to guide the selection of an optimal penicillin regimen (i.e., the dose, duration, and preparation). Substantially fewer data are available for nonpenicillin regimens.

Recommended Regimen for Adults

- Benzathine penicillin G 2.4 million units intramuscularly in a single dose

Note: Recommendations for treating pregnant women and HIV-infected patients for syphilis are discussed in separate sections.

Recommended Regimen for Children

After the newborn period, children with syphilis should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether

such children have congenital or acquired syphilis (see Congenital Syphilis). Children with acquired primary or secondary syphilis should be evaluated (e.g., through consultation with child-protection services) (see Sexual Assault or Abuse of Children) and treated by using the following pediatric regimen.

- Benzathine penicillin G 50,000 units/kg intramuscularly, up to the adult dose of 2.4 million units in a single dose

Other Management Considerations

All patients who have syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be retested for HIV after 3 months if the first HIV test result was negative.

Patients who have syphilis and who also have symptoms or signs suggesting neurologic disease (e.g., meningitis) or ophthalmic disease (e.g., uveitis) should have an evaluation that includes CSF analysis and ocular slit-lamp examination. Treatment should be guided by the results of this evaluation.

Invasion of CSF by T. pallidum accompanied by CSF abnormalities is common among adults who have primary or secondary syphilis. However, neurosyphilis develops in only a limited number of patients after treatment with the penicillin regimens recommended for primary and secondary syphilis. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present, CSF analysis is not recommended for routine evaluation of patients who have primary or secondary syphilis.

Follow-Up

Treatment failure can occur with any regimen. However, assessing response to treatment often is difficult, and definitive criteria for cure or failure have not been established. Nontreponemal test titers may decline more slowly for patients who previously had syphilis. Patients should be reexamined clinically and serologically 6 months and 12 months following treatment; more frequent evaluation may be prudent if follow-up is uncertain.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer (i.e., compared with the maximum or baseline titer at the time of treatment) probably failed treatment or were reinfected. These patients should be re-treated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with T. pallidum, a CSF analysis also should be performed. A recent clinical trial demonstrated that 15% of patients with early syphilis treated with the recommended therapy will not achieve a two dilution decline in nontreponemal titer used to define response at 1 year following treatment.

Failure of nontreponemal test titers to decline fourfold within 6 months after therapy for primary or secondary syphilis is indicative of probable treatment failure. Persons for whom titers remain serofast should be reevaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these

patients should have additional clinical and serologic follow-up. HIV-infected patients should be evaluated more frequently (i.e., at 3-month intervals instead of 6-month intervals). If additional follow-up cannot be ensured, re-treatment is recommended. Because treatment failure may be the result of unrecognized central nervous system infection, some specialists recommend CSF examination in such situations.

When patients are re-treated, most STD specialists recommend administering weekly injections of benzathine penicillin G 2.4 million units intramuscularly for 3 weeks, unless CSF examination indicates that neurosyphilis is present. In rare instances, serologic titers do not decline despite a negative CSF examination and a repeated course of therapy. Additional therapy or repeated CSF examinations are not warranted in these circumstances.

Management of Sex Partner

See General Principles, Management of Sex Partners above.

Special Considerations

Penicillin Allergy. Data to support the use of alternatives to penicillin in the treatment of early syphilis are limited. However, several therapies might be considered effective in nonpregnant, penicillin-allergic patients who have primary or secondary syphilis. Doxycycline (100 mg orally twice daily for 14 days) and tetracycline (500 mg four times daily for 14 days) are regimens that have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone is effective for treating early syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined. However, some specialists recommend 1 gram daily either intramuscularly or intravenously for 8-10 days. Preliminary data suggest that azithromycin may be effective as a single oral dose of 2 grams. Because the efficacy of these therapies is not well documented, close follow-up of persons receiving these therapies is essential. The use of any of these therapies in HIV-infected persons has not been studied; the use of doxycycline, ceftriaxone, and azithromycin among such persons must be undertaken with caution.

Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin. Skin testing for penicillin allergy may be useful in some circumstances in which the reagents and expertise are available to perform the test adequately (see Management of Patients Who Have a History of Penicillin Allergy).

Pregnancy. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection. See Syphilis Among HIV-Infected Persons below.

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Patients who have latent syphilis and who acquired syphilis within the preceding year are classified as having early latent syphilis. Patients can be diagnosed as having early latent syphilis if, within the year preceding the evaluation, they had a) a documented seroconversion, b) unequivocal symptoms of primary or secondary syphilis, or c) a sex partner documented to have primary, secondary, or early latent syphilis. Patients who have latent syphilis of unknown duration should be managed as if they have late latent syphilis. Nontreponemal serologic titers usually are higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers. All patients with latent syphilis should have careful examination of all accessible mucosal surfaces (i.e., the oral cavity, the perineum in women, and underneath the foreskin in uncircumcised men) to evaluate for internal mucosal lesions. All patients who have syphilis should be tested for HIV infection.

Treatment

Treatment of latent syphilis usually does not affect transmission and is intended to prevent occurrence or progression of late complications. Although clinical experience supports the effectiveness of penicillin in achieving these goals, limited evidence is available for guidance in choosing specific regimens.

The following regimens are recommended for nonallergic patients who have normal CSF examinations (if performed).

Recommended Regimens for Adults

Early Latent Syphilis

- Benzathine penicillin G 2.4 million units intramuscularly in a single dose.

Late Latent Syphilis or Latent Syphilis of Unknown Duration

- Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscularly each at 1-week intervals

After the newborn period, children with syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether children have congenital or acquired syphilis. Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens (see Sexual Assault or Abuse of Children). These regimens are for non-allergic children who have acquired syphilis and who have normal CSF examination results.

Recommended Regimens for Children

Early Latent Syphilis

- Benzathine penicillin G 50,000 units/kg intramuscularly, up to the adult dose of 2.4 million units in a single dose

Late Latent Syphilis or Latent Syphilis of Unknown Duration

- Benzathine penicillin G 50,000 units/kg intramuscularly, up to the adult dose of 2.4 million units, administered as three doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)

Other Management Considerations

All patients who have latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis, gumma, and iritis). Patients who have syphilis and who demonstrate any of the following criteria should have a prompt CSF examination:

- neurologic or ophthalmic signs or symptoms
- evidence of active tertiary syphilis (e.g., aortitis, gumma, and iritis)
- treatment failure
- HIV infection with late latent syphilis or syphilis of unknown duration

If dictated by circumstances and patient preferences, a CSF examination may be performed for patients who do not meet these criteria. Some specialists recommend performing a CSF examination on all patients who have latent syphilis and a nontreponemal serologic test of $\geq$1:32. The risk of neurosyphilis in this circumstance is unknown. If a CSF examination is performed and the results indicate abnormalities consistent with neurosyphilis, the patient should be treated for neurosyphilis (see Neurosyphilis).

If a patient misses a dose of penicillin in the course of weekly therapy for late syphilis, the appropriate course of action is unclear. Pharmacologic considerations suggest that an interval of 10--14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses should not be considered acceptable for pregnant patients receiving therapy for late latent syphilis; pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up. Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. Patients with a normal CSF examination should be re-treated for latent syphilis if a) titers increase fourfold, b) an initially high titer ($\geq$1:32) fails to decline at least fourfold (i.e., two dilutions) within 12-24 months of therapy, or c) signs or symptoms attributable to syphilis develop. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers may still not decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear.

Management of Sex Partners. See General Principles, Management of Sex Partners above.

Special Considerations

Penicillin Allergy. The effectiveness of alternatives to penicillin in the treatment of latent syphilis has not been well documented. Nonpregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to therapies recommended as alternatives to penicillin for the treatment of primary and secondary syphilis. The only acceptable alternatives for the treatment of late latent syphilis or latent syphilis of unknown duration are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily) both for 28 days. These therapies should be used only in conjunction with close serologic and clinical follow-up. The efficacy of these alternative regimens in HIV-infected persons has not been studied, and thus must be considered with caution.

Pregnancy. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection. See Syphilis Among HIV-Infected Persons below.

Tertiary Syphilis

Tertiary syphilis refers to gumma and cardiovascular syphilis, but not to all neurosyphilis. Patients who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen

- Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscularly each at 1-week intervals

Other Management Considerations

Patients who have symptomatic late syphilis should be given a CSF examination before therapy is initiated. Some providers treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. The complete management of patients who have cardiovascular or gummatous syphilis is beyond the scope of these guidelines. These patients should be managed in consultation with an infectious diseases specialist.

Follow-Up. Limited information is available concerning clinical response and follow-up of patients who have tertiary syphilis.

Management of Sex Partners. See General Principles, Management of Sex Partners above.

Special Considerations

Penicillin Allergy. Patients allergic to penicillin should be treated according to treatment regimens recommended for late latent syphilis.

Pregnancy. Pregnant patients who are allergic to penicillin should be desensitized, if necessary, and treated with penicillin. (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection. See Syphilis Among HIV-Infected Persons below.

Neurosyphilis

Treatment

Central nervous system disease can occur during any stage of syphilis. A patient who has clinical evidence of neurologic involvement with syphilis (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis) should have a CSF examination.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis; patients with these symptoms should be treated according to the recommendations for patients with neurosyphilis. A CSF examination should be performed for all such patients to identify those with abnormalities who should have follow-up CSF examinations to assess treatment response.

Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the following regimen.

Recommended Regimen

- Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units intravenously every 4 hours or continuous infusion, for 10-14 days

If compliance with therapy can be ensured, patients may be treated with the following alternative regimen.

Alternative Regimen

- Procaine penicillin 2.4 million units intramuscularly once daily

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- Probenecid 500 mg orally four times a day, both for 10-14 days.

The durations of the recommended and alternative regimens for neurosyphilis are shorter than that of the regimen used for late syphilis in the absence of neurosyphilis. Therefore, some specialists administer benzathine penicillin, 2.4 million units intramuscularly once per week for up to 3 weeks after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations

Other considerations in the management of patients who have neurosyphilis are as follows.

- All patients who have syphilis should be tested for HIV.
- Many specialists recommend treating patients who have evidence of auditory disease caused by syphilis in the same manner as patients who have neurosyphilis, regardless of CSF examination results. Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven beneficial.

Follow-Up. If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the VDRL-CSF or CSF protein after therapy; however, changes in these two parameters are slower, and persistent abnormalities may be less important. If the cell count has not decreased after 6 months, or if the CSF is not normal after 2 years, re-treatment should be considered.

Management of Sex Partners. See General Principles, Management of Sex Partners above.

Special Considerations

Penicillin Allergy. Ceftriaxone can be used as an alternative treatment for patients with neurosyphilis, although the possibility of cross-reactivity between this agent and penicillin exists. Some specialists recommend ceftriaxone 2 grams daily either intramuscularly or intravenously for 10-14 days. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, if concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, the patient should obtain skin testing to confirm penicillin allergy and, if necessary, be desensitized and managed in consultation with a specialist.

Pregnancy. Pregnant patients who are allergic to penicillin should be desensitized, if necessary, and treated with penicillin (see Syphilis During Pregnancy below).

HIV Infection. See Syphilis Among HIV-Infected Persons below.

Syphilis Among HIV-Infected Persons

Diagnostic Considerations

Unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most reports have involved serologic titers that were higher than expected, but false-negative serologic test results and delayed appearance of seroreactivity also have been reported. However, aberrant serologic responses are uncommon, and most specialists believe that both treponemal and non-treponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfected with T. pallidum and HIV.

When clinical findings are suggestive of syphilis, but serologic tests are nonreactive or the interpretation is unclear, alternative tests (e.g., biopsy of a lesion, darkfield examination, or direct fluorescent antibody staining of lesion material) may be useful for diagnosis.

Neurosyphilis should be considered in the differential diagnosis of neurologic disease in HIV-infected persons.

Treatment

Compared with HIV-negative patients, HIV-positive patients who have early syphilis may be at increased risk for neurologic complications and may have higher rates of treatment failure with currently recommended regimens. The magnitude of these risks, although not defined precisely, is likely minimal. No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients. Careful follow-up after therapy is essential.

Primary and Secondary Syphilis Among HIV-Infected Persons

Treatment

Treatment with benzathine penicillin G, 2.4 million units intramuscularly in a single dose is recommended. Some specialists recommend additional treatments (e.g., benzathine penicillin G administered at 1-week intervals for 3 weeks, as recommended for late syphilis) in addition to benzathine penicillin G 2.4 million units intramuscularly.

Other Management Considerations

Because CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in patients with early syphilis and in persons with HIV infection, the clinical and prognostic significance of such CSF abnormalities in HIV-infected persons with primary or secondary syphilis is unknown. Although most HIV-infected persons respond appropriately to standard benzathine penicillin therapy, some specialists recommend intensified therapy when central nervous system syphilis is suspected in these persons. Therefore, some specialists recommend CSF examination before treatment of HIV-infected persons with early syphilis, with follow-up CSF examination following treatment in persons with initial abnormalities.

Follow-Up. HIV-infected patients should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy. Although of unproven benefit, some specialists recommend a CSF examination 6 months after therapy.

HIV-infected patients who meet the criteria for treatment failure should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and re-treatment). Cerebrospinal fluid examination and re-treatment also should be strongly considered for patients whose nontreponemal test titers do not

decrease fourfold within 6-12 months of therapy. Most specialists would re-treat patients with benzathine penicillin G administered as three doses of 2.4 million units intramuscularly each at weekly intervals, if CSF examinations are normal.

Special Considerations

Penicillin Allergy. Penicillin-allergic patients who have primary or secondary syphilis and HIV infection should be managed according to the recommendations for penicillin-allergic, HIV-negative patients. The use of alternatives to penicillin has not been well studied in HIV-infected patients.

Latent Syphilis Among HIV-Infected Persons

Diagnostic Considerations

HIV-infected patients who have early latent syphilis should be managed and treated according to the recommendations for HIV-negative patients who have primary and secondary syphilis. HIV-infected patients who have either late latent syphilis or syphilis of unknown duration should have a CSF examination before treatment.

Treatment

Patients with late latent syphilis or syphilis of unknown duration and a normal CSF examination can be treated with benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks. Patients who have CSF consistent with neurosyphilis should be treated and managed as patients who have neurosyphilis (see Neurosyphilis).

Follow-Up. Patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. If, at any time, clinical symptoms develop or nontreponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly. If in 12--24 months the nontreponemal titer does not decline fourfold, the CSF examination should be repeated and treatment administered accordingly.

Special Considerations

Penicillin Allergy. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy). The efficacy of alternative non-penicillin regimens in HIV-infected persons has not been studied.

Syphilis During Pregnancy

All women should be screened serologically for syphilis at the first prenatal visit. In populations in which prenatal care is not optimal, RPR-card test screening and treatment (if the RPR-card test is reactive) should be performed at the time a pregnancy is confirmed. For communities and populations in which the prevalence of syphilis is high or for patients at high risk, serologic testing should be

performed twice during the third trimester, at 28 weeks' gestation, and at delivery in addition to routine early screening. Some states mandate screening at delivery for all women. Any woman who delivers a stillborn infant after 20 weeks' gestation should be tested for syphilis. No infant should leave the hospital if maternal serologic status has not been determined at least once during pregnancy and preferably again at delivery.

Diagnostic Considerations

Seropositive pregnant women should be considered infected unless an adequate treatment history is documented in the medical records and sequential serologic antibody titers have declined.

Treatment

Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection. Evidence is insufficient to determine whether the specific, recommended penicillin regimens are optimal.

Recommended Regimen

- Treatment during pregnancy should consist of the penicillin regimen appropriate for the stage of syphilis

Other Management Considerations

Some specialists recommend additional therapy in some patients. A second dose of benzathine penicillin 2.4 million units intramuscularly may be administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis. In the second half of pregnancy, management and counseling may be facilitated by a sonographic fetal evaluation for congenital syphilis, but this should not delay therapy. Sonographic signs of fetal syphilis (i.e., hepatomegaly, ascites, and hydrops) indicate a greater risk for fetal treatment failure; such cases should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations.

Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction. These women should be advised to seek obstetric attention after treatment if they notice any contractions or decrease in fetal movements. Although stillbirth is a rare complication of treatment, concern about this complication should not delay necessary treatment. All patients who have syphilis should be offered testing for HIV infection.

Follow-Up. Coordinated prenatal care, treatment follow-up, and syphilis case management are important in the management of pregnant women with syphilis. Serologic titers should be repeated in the third trimester and at delivery. Serologic titers may be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high. The clinical and antibody response should be appropriate for the stage of disease. Most women

will deliver before their serologic response to treatment can be assessed definitively.

Management of Sex Partners. See General Principles, Management of Sex Partners above.

Special Considerations

Penicillin Allergy. No alternatives to penicillin have been proved effective for treatment of syphilis during pregnancy. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Skin testing may be helpful (see Management of Patients Who Have a History of Penicillin Allergy).

Tetracycline and doxycycline should not used during pregnancy. Erythromycin should not be used, because it does not reliably cure an infected fetus. Data are insufficient to recommend azithromycin or ceftriaxone.

HIV Infection. See Syphilis Among HIV-Infected Persons.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Throughout the 2002 guideline document, the evidence used as the basis for specific recommendations is discussed briefly. More comprehensive, annotated discussions of such evidence will appear in background papers that will be published in a supplement issue of the journal Clinical Infectious Diseases.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis, treatment, and follow-up of patients with genital ulcers.
- Decreased transmission of syphilis and herpes simplex virus to infants and sexual partners.
- Decreased risk for HIV infection.

Subgroups Most Likely to Benefit:

Young, sexually active patients

POTENTIAL HARMS

- Allergic and other adverse reactions to acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described previously.
- In immunocompromised patients, valacyclovir in doses of 8 g per day has been associated with a syndrome resembling either hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.
- The Jarish-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, and other symptoms that usually occurs within the first 24 hours after any therapy for syphilis. Patients should be informed about this possible adverse reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress among pregnant.

Subgroups Most Likely to be Harmed:

- The safety of azithromycin for pregnant and lactating women has not been established.
- The safety of acyclovir and valacyclovir therapy in pregnant women has not been established.
- Prenatal exposure to valacyclovir and famciclovir is too limited to provide useful information on pregnancy outcomes.
- Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarish-Herxheimer reaction. These women should be advised to seek obstetric attention after treatment if they notice any contractions or decrease in fetal movements. Stillbirth is a rare complication of treatment, but concern for this complication should not delay necessary treatment.
- Tetracycline and doxycycline usually are not used during pregnancy.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Ciprofloxacin is contraindicated for pregnant and lactating women.
- Pregnancy is a relative contraindication to the use of sulfonamides.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations were developed in consultation with public- and private-sector professionals knowledgeable in the treatment of patients with sexually transmitted diseases (STDs). They are applicable to various patient-care settings, including family planning clinics, private physicians' offices, managed care organizations, and other primary-care facilities. When using these guidelines, the disease prevalence and other characteristics of the medical practice setting should be considered. These recommendations should be regarded as a source of clinical guidance and not as standards or inflexible rules. These guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are important in sexually transmitted disease/human immunodeficiency virus (STD/HIV) prevention.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Diseases characterized by genital ulcers. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2002 May 10;51(RR-6):11-25.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1993 (revised 2002 May 10)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

GUIDELINE DEVELOPER COMMENT

These guidelines for the treatment of patients who have sexually transmitted diseases (STDs) were developed by the Centers for Disease Control and Prevention (CDC) after consultation with a group of professionals knowledgeable in the field of STDs who met in Atlanta on September 26--28, 2000.

SOURCE(S) OF FUNDING

United States Government

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Not stated

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The information in this report updates the "1998 Sexually Transmitted Diseases Treatment Guidelines" (MMWR 1998;47[No. RR-1]).

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML version
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Workowski KA, Levine WC, Wasserheit JN. U.S. Centers for Disease Control and Prevention guidelines for the treatment of sexually transmitted diseases: an opportunity to unify clinical and public health practice. Ann Intern Med. 2002 Aug 20;137(4):255-62. Electronic copies: Available through Annals of Internal Medicine Online.
- Sexually Transmitted Diseases Treatment Guidelines 2002 for PDA or Palm OS. Available from the CDC National Prevention Information Network (NPIN) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 2002.

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